

## Cognitive and Motivational Functions of the Human Prefrontal Cortex

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When Luria published *Higher Cortical Functions in Man* in 1966, he was forced to concede that "... in considering the pathology of the frontal lobes we are dealing with a branch of modern neurology where the facts ... are still too few and often contradictory" (Luria 1966, p. 218). Nonetheless, based on clinical observation of countless patients with varying degrees of damage to frontal regions of cortex, Luria was able to differentiate between three broad regions of the frontal lobes with clearly distinguishable contributions to human cognition: the premotor division, the prefrontal convex division, and the mediobasal or orbital division (Figure 4-1). According to Luria, the central features of damage to these three regions are, respectively, "disturbance of skilled movement and a disintegration of complex kinetic melodies. . . , lack of continuous comparison between the plan of action and the results actually attained. . . , [and] gross changes in the affective sphere leading to disturbances of character and personality" (p. 293). Although this early presentation of frontal lobe function was, of necessity, extremely broad and nonspecific, it nonetheless anticipated the findings of modern work using both lesion data and functional neuroimaging techniques in healthy individuals.

Studies of brain-injured patients by Luria and others provided convincing demonstrations that different regions of the cortex are associated with different psychological functions. However, the question of how psychological functions map onto specific brain regions is a difficult one for a variety of reasons. One is that "functions" may be defined and categorized in a number of ways and at a

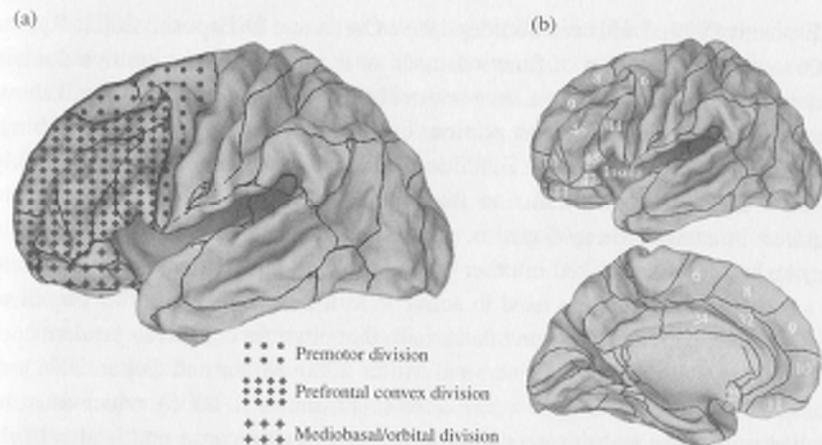


FIGURE 4-1. (a) The three divisions of human prefrontal cortex described by Luria (1966). (b) Brodmann's area labels for the lateral and medial surfaces of the prefrontal cortex (labels from CARET software; Van Essen, et al. 2001).

number of levels of generality. Finding semantic categories that "carve nature at its joints" is difficult because the natural ways of segmenting concepts in human language may not be those respected by the brain. For example, basic categories of emotion such as "fear," "anger," and "disgust" are easily recognizable as coherent concepts across cultures (Ekman, Sorenson, and Friesen 1969; Ekman 1992), but patterns of emotional alterations with brain damage (e.g., Hornak, et al. 2003) and brain activity in recent neuroimaging studies (Barrett and Wager 2006) do not seem to respect these categories. Luria argued that even "... such an apparently simple function as respiration is actually a complex functional system, effected by a differential dynamic arrangement of nerve cells belonging to different levels of the nervous system" (p. 25); thus, even in this simple example, the apparent function at the behavioral level (respiration) cannot be localized to a discrete brain region. However, in attempting to understand the brain, cognitive neuroscientists are searching for psychological concepts that best describe different areas of the cortex. A satisfactory description would ultimately associate particular cortical regions with specific "atomic elements" of cognitive processing that are used in different combinations across many tasks (e.g., in the Adaptive Control of Thought-Rational (ACT-R) model of cognition; Anderson, 1993).

Another issue that emerges is with assigning functions to areas of the brain based on experimental results from a single domain of study. For example, activation of dorsolateral prefrontal cortex (DLPFC; part of the prefrontal convex division described by Luria) in working memory (WM) tasks is commonly interpreted as reflecting active manipulation of the contents of WM (e.g., Rypma and

D'Esposito 1999; Smith and Jonides 1999; Curtis and D'Esposito 2003; Rypma 2006)—an interpretation of function made at the level of the cognitive domain under study. Although this is a very reasonable characterization, as we will show, activation of DLPFC (or at least portions of it) also occurs during studies of long-term memory (LTM), response inhibition, and task-switching (and quite possibly in other domains as well). Active manipulation of the contents of WM is not required in each of these domains, suggesting that the function of this region may be better characterized in other terms. An alternative characterization could be a more general function used in active WM maintenance and other cognitive control tasks, such as activation of task rules that provides context-dependent control over behavior (Asaad, Rainer, and Miller 2000; Miller and Cohen 2001), or alternatively the refreshing of information (Johnson, et al. 2005), which must be applied repeatedly and prospectively during WM maintenance and is also likely to be involved in maintaining task set in response-inhibition tasks. We return to these questions later in the chapter.

Despite the enormous amount of empirical research carried out on the functional organization of the frontal lobes since Luria's time, there are still very few frontal cortical regions whose functions can be specified with a high degree of certainty. One reason for this may be that a satisfactory characterization of function requires reliable information about the various kinds of task demands that do and do not produce deficits after lesions, or activity changes measured with neuroimaging, in a given region. In the example above, comparison of brain activity patterns across different types of tasks provided some basis for comparing alternative conceptualizations. In the remainder of this chapter, we continue along these lines and use evidence from meta-analyses of neuroimaging studies across a wide range of tasks to develop a synopsis of some of the current understanding of the functional organization of prefrontal cortex.

### Meta-analyses

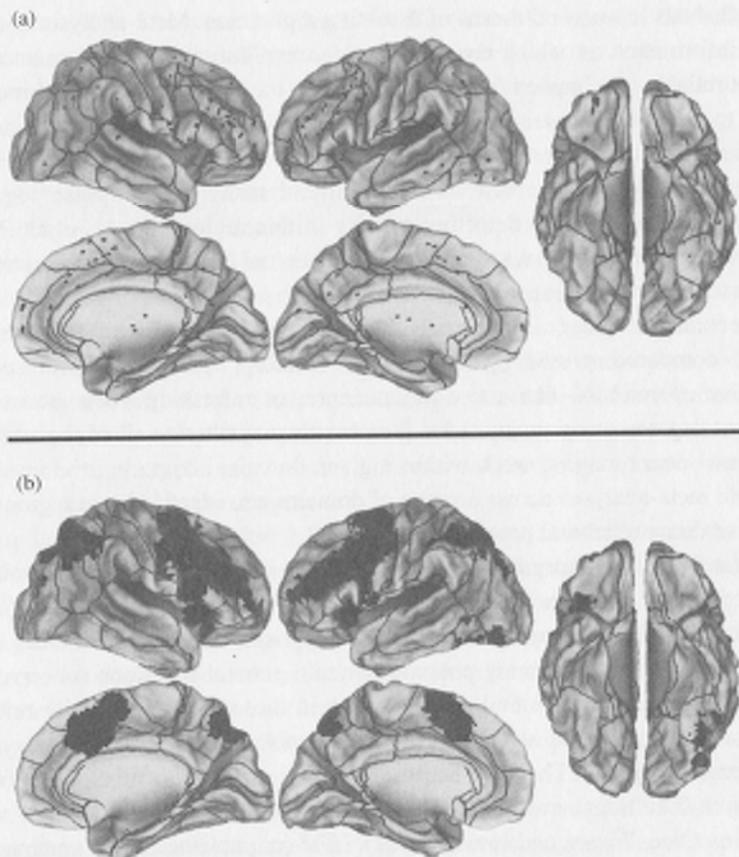
Meta-analysis of neuroimaging studies, particularly functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), is an important tool in understanding functional brain organization that complements studies of patients with brain damage and other methodologies such as event-related potentials, transcranial magnetic stimulation, animal lesion studies, and intracranial recording. Ultimately, all of these methods provide a unique window into cognitive function, and each makes important contributions. An advantage of using meta-analysis to summarize neuroimaging studies is that there have now been hundreds of such studies published on similar tasks in a range of domains, and meta-analyses can identify consistent and replicable results across different laboratories, scanners, and study designs. Activation of a region in a single study does not provide strong evidence unless it is replicated across laboratories, and

meta-analysis is a natural means of assessing replication. Meta-analysis also provides information on which regions are not active during task performance that cannot reliably be obtained from single studies. If a single study of LTM retrieval failed to find orbitofrontal cortex (OFC) activity, for example, this negative result would mean little: power in most fMRI and PET studies is extremely low when appropriate statistical corrections are used, and many scanner/pulse sequence combinations are poor at detecting activity in this region (Wager, et al. 2007). However, if no (or very few) studies of LTM ever find OFC, this provides stronger evidence for functional specialization.

A second advantage of meta-analysis is that results across many task domains can be compared, providing the ability to develop hypotheses about specific cognitive operations—like active maintenance, or refreshing—that are used to different degrees across many tasks. Because they synthesize all of the available functional neuroimaging work within a given domain, comparing the results of multiple meta-analyses across a range of domains can identify brain regions that subserve domain-general processes.

To date, our laboratory has produced meta-analyses of functional neuroimaging work across a number of domains relevant to the function of prefrontal cortex. Consequently, in this chapter we will use comparisons of these meta-analyses as a starting point for discussing potential domain-general functions subserved by different regions of prefrontal cortex, filling in these discussions with relevant lesion and animal work, as well as the results of individual neuroimaging studies where appropriate. The meta-analyses under consideration are of WM (Wager and Smith 2003), task-switching (Wager, Jonides, and Reading 2004), response inhibition (Nee, Wager, and Jonides 2007), LTM (unpublished data), and emotion (Wager, et al. 2003; Wager, et al. 2008). The meta-analyses use as data the spatial locations of peak activations, which are typically reported in neuroimaging publications for one or more comparisons between task performance and control conditions. Statistical tests are performed to locate consistently activated regions; that is, those regions in which many peaks across different studies are reported. In Figure 4-2, an example of this process is briefly presented for studies reporting peaks during WM tasks with an executive component. The testing procedure involves making a map across 200,000 or so "voxels" in the brain (sampled at  $2 \times 2 \times 2$  mm resolution) of the number of studies that report peaks in the neighborhood (typically 10–15 mm) of each voxel, and using simulations to locate regions where reported peaks are clustered densely enough to distinguish the cluster from the background noise (peaks scattered across the brain with no apparent spatial pattern). These methods are summarized in the individual papers and in a recent paper on meta-analysis methods (Wager, Lindquist, and Kaplan 2007), and we do not review them in detail here.

To evaluate the extent to which regions in the prefrontal cortex are activated in multiple domains, we produced a set of conjunction images—that is, brain



**FIGURE 4-2.** Example of how meta-analytic results are obtained in neuroimaging studies. Each of the points in (a) represents an activation peak reported in an individual study of executive WM. Spatial smoothing is then applied to each of these peaks, and statistical analyses are carried out to determine, for each voxel in the brain, whether there is consistent evidence for activation of that voxel across studies. The activated regions in (b) represent the areas of significant activation based on the peaks displayed in (a).

volumes of activated voxels that include only those voxels that are activated in a set (two or more) of analyses of interest—for each of the possible combinations of meta-analysis data sets. Because there is some degree of spatial variability inherent in functional imaging data, we expanded the activated regions in each of the meta-analyses by 2.5 mm in order to better detect regions of prefrontal cortex that are involved in multiple domains. Finally, we mapped each of these images onto surface renderings of the PALS atlas (Van Essen 2005) using Caret software (Van Essen, et al. 2001) to produce the figures presented throughout this chapter.

### Meta-analytic data sets

In discussing the findings of these meta-analyses, it is important to be aware of the kinds of studies that went into each data set. We present data from two contrasts in the WM meta-analysis (Wager and Smith 2003): WM storage and WM executive. Identified peaks in the WM storage contrast reflect consistent activations across study conditions that require the maintenance of information in WM compared with a non-mnemonic baseline, whereas the WM executive contrast reflects activations across studies that involve manipulation of the contents of WM, continuous updating of the information held in WM (e.g., in an n-back task), or memory for the order of items in the memory set. Importantly, the WM executive contrast reflects only those regions that are significantly more active during WM executive tasks than during WM storage.

The inhibition data reported here (Nee, Wager, and Jonides 2007) reflect consistent activations across studies of the Stroop, flanker, go/no-go, stimulus-response compatibility, Simon, and stop signal tasks. Though a thorough description of each of these tasks is beyond the scope of this chapter, they all require either the inhibition of an already-initiated response (a paradigmatic case being the stop signal task, where in some trials a signal to inhibit responding is presented shortly after a stimulus that would otherwise be responded to) or the inhibition of a prepotent response, for example the Stroop task in which subjects must overcome the prepotent tendency to read words in order to correctly name the color the words are printed in. Importantly, in this latter set of tasks, it is generally presumed that the need to inhibit an already-initiated response also occurs, insofar as the prepotent response is likely to be initiated and later inhibited on at least some trials.

The task-switching meta-analysis (Wager, Jonides, and Reading 2004) included studies in which the contrast of interest reflected a condition in which participants had to change stimulus-response (S-R) contingencies in some prespecified way in order to perform the task successfully. This could include changes in the spatial location of stimuli that were to be responded to, changes in the dimension of a stimulus to which responses are to be made (e.g., shifting from responding based on stimulus color to responding based on shape), reversal or reassignment of response contingencies, or conditions in which the stimulus set was changed.

For the emotion meta-analysis (Wager, et al. 2008) we report on regions that show greater activation during the experience of emotion than during the perception of emotion (i.e., viewing emotional faces or scenes that are unlikely to evoke a strong emotional response in participants compared with conditions in which participants generate strong feeling states in response to stimuli of various kinds).

Finally, the LTM data set reported here is a preliminary analysis of 165 studies of LTM. Reported peaks reflect regions that are significantly active across this data set, which included studies of either encoding or retrieval (or both) of information from LTM compared with an appropriate baseline.

## Hierarchies of prefrontal function

In the following sections, we discuss some putative functions subserved by specific regions of the prefrontal cortex, beginning with those regions activated in the broadest range of cognitive domains (across our meta-analytic data sets) and moving to those activated in the fewest domains, and finally discussing those regions activated during both cognition and emotional experience. We will then argue that the available data suggest that processing within the prefrontal cortex proceeds in an approximately hierarchical fashion, with posterior premotor regions maintaining specific S-R associations in order to direct motor behavior in a task-appropriate fashion, the inferior frontal junction (see later) establishing or switching between different S-R mappings depending on the current context, DLPFC engaging in top-down biasing of representations in posterior cortices, and anterior lateral prefrontal cortex involved in higher-order or subgoal processing. At the "top" of this network are the OFC and rostral medial prefrontal cortex, which assess the potential reward value of stimuli in the environment and, via the anterior insula and the dorsal medial prefrontal cortex, direct motivated cognition and behavior in a manner that maximizes expected reward. A list of the prefrontal regions discussed here, along with a brief description of their putative function and the meta-analytic data sets in which they are significantly activated, is presented in Table 4-1.

## Common activations across cognitive domains

A number of regions were found to be active in all or most of the cognitive domains for which we have meta-analytic data, suggesting that each of these regions subserve a domain-general function that is deployed under a variety of task conditions. These results echo an early report by Duncan and Owen (2000) that a wide range of tasks, including WM, response conflict (e.g., Stroop), novel task learning, and tasks involving perceptual difficulty activated a common set of regions—dorsal anterior cingulate and mid-dorsolateral and mid-ventrolateral prefrontal cortex bilaterally—very similar to those activated in our analysis. We now discuss each of these regions in turn.

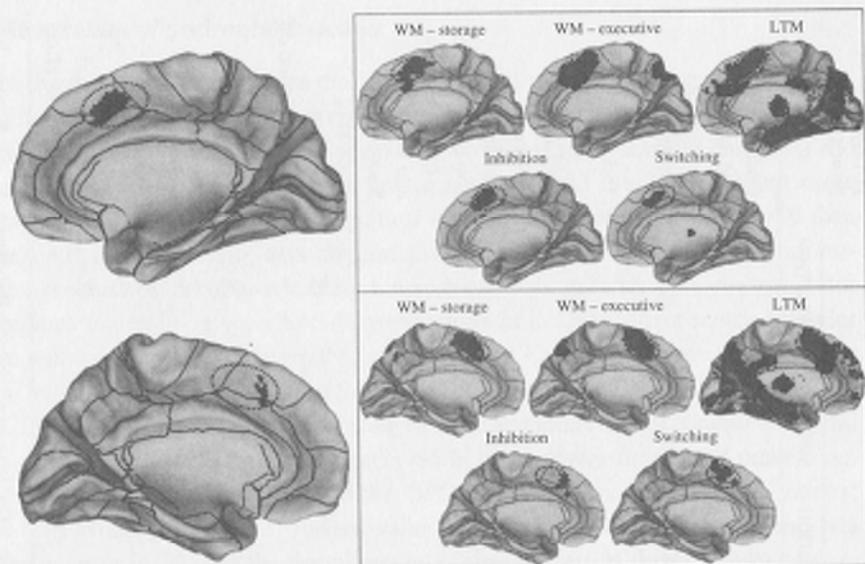
### Dorsal Medial Junction

As shown in Figure 4-3, all of the included tasks show bilateral activation of a medial prefrontal cortex region, which we have termed the dorsal medial junction (DMJ) to refer to a collection of regions homologous to macaque rostral cingulate motor area (CMAr) and presupplementary motor areas (pre-SMA; Picard and Strick 1996) because it lies at the interface of medial Brodmann's areas (BAs) 6

TABLE 4-1. List of regions with significant activations in multiple domains

REGION	BAS	TASK DOMAINS						PUTATIVE FUNCTION
		LATERALIZATION	WM (s)	WM (e)	LTM	INHIBITION	SWITCHING	
Dorsal medial junction	6/8/32	B	X	X	X	X	X	Energization and motor preparedness
Inferior frontal junction	6/44/46	L	X	X	X	X	X	Task-setting
Inferior frontal junction	6/44/46	R	X	X	X	X	X	Task-setting
Posterior IFG	44/45/46	L	X	X	X	X	X	Task-setting
Posterior IFG	44/45/46	R	X	X	X	X	X	Response inhibition
Dorsal lateral PFC	46	B	X	X	X	X	X	Top-down biasing
Middle and anterior IFG	45/47	L	X	X	X	X	X	Semantic retrieval and selection
Rostral lateral PFC	10	B	X	X	X	X	X	Subgoal processing
Anterior insula	—	L	X	X	X	X	X	Directing cognition based on reward value
Anterior insula	—	R	X	X	X	X	X	Task-setting
Orbitofrontal cortex	11	L	X	X	X	X	X	Valuations of reward
Orbitofrontal cortex	11	R	X	X	X	X	X	Task-setting
Dorsomedial PFC	9	B	X	X	X	X	X	Generation and regulation of affect

Note: BAs, Brodmann's areas; WM (s), working memory storage; WM (e), working memory executive; LTM, long-term memory; B, bilateral; L, left; R, right; IFG, inferior frontal gyrus; PFC, prefrontal cortex.



**FIGURE 4-3.** Conjunction images of the meta-analytic results for WM storage, WM executive, LTM, inhibition, and task-switching shown on the medial surface of the brain. Insets show the activated regions in each individual domain. The region indicated with a dotted line is the DMJ region discussed in the text.

and 8 and the dorsal portion of BA 32. Although activation of this area of cortex is frequently referred to as activation of anterior cingulate cortex (ACC) in the literature, we prefer the term DMJ because the data from our meta-analyses show that the activated region frequently includes a substantial portion of noncingulate cortex and typically only includes the most caudal portion of BA 32, a rather restricted portion of ACC (see Figure 4-3). Furthermore, when authors refer to ACC, it is frequently unclear precisely which area of the ACC they are referring to. Given that the region identified in our meta-analyses is consistently activated in WM storage, WM tasks that require executive processing in addition to "simple" maintenance, LTM, response inhibition, and task-switching, it is probably true that in most cases pertaining to cognitive tasks authors are referring to the same region of cortex identified in our meta-analyses.

It is beyond the purview of this chapter to enumerate the wide array of domain-specific functions that have been attributed to the ACC. Suffice it to say that activation of this region occurs in an astonishing array of cognitive tasks, and there does not seem to be general agreement about the functional role of this area of the brain. An early review of 107 PET studies (Paus, et al. 1998) examined a number of potential predictors of activity in this region and concluded that the best predictor of activation was "task difficulty." Indeed, the fact that it is activated in all of the cognitive tasks for which we have meta-analytic data strongly

suggests that it plays a domain-general role in cognition that is deployed in a wide variety of situations.

One interpretation of the role of the DMJ consistent with the range of domains in which it is activated in our meta-analyses comes from human lesion work by Stuss and Alexander (2007). Based on behavioral data from patients with lesions in a variety of frontal sites across a number of cognitive tasks, these authors propose that patients with lesions of superior medial frontal cortex, which overlaps almost entirely with the DMJ region identified in our meta-analyses, exhibit a specific deficit in "energization"—the ability to refresh task-relevant perceptual and motor representations in the absence of specific cues. Observing that neural activity generally diminishes without continuous input, these authors propose that "in the absence of external triggers or motivational conditions to optimize responding, lower level perceptual or motor schemata would have to be energized or re-energized when activation becomes low . . ." (p. 904). Thus, energization, and consequently the DMJ, is essential for speeded, optimized performance in cognitive tasks where an attentional set facilitates performance.

There are a number of behavioral findings reported by Stuss and Alexander (2007) that are selective to damage in this region compared with damage in other regions of frontal cortex (and not predicted simply by the extent of lesion). First, patients with lesions in this area exhibit slower reaction times (RTs) but normal error rates in a range of RT tasks that vary in complexity, independent of fatigue or motivation to perform the task, and consistent with a difficulty in energizing or otherwise maintaining the preparation to respond. Perhaps most striking among these findings is the fact that patients with lesions in this area, but not other cortical areas, showed no RT benefit when a warning stimulus appeared 3 seconds prior to target stimuli, again suggesting a failure to energize cognitive resources relevant to the task at hand. In addition, patients with superior medial prefrontal lesions uniquely failed to produce a greater number of words in standard verbal fluency tasks in the last 45 seconds of the task compared with that in the first 30 seconds, suggesting that relative to other patients they were unable to maintain performance over time. Finally, these patients show greater RTs and many more errors in the incongruent condition of the Stroop task, a finding interpreted as indicating that the patients were unable to maintain the intended response.

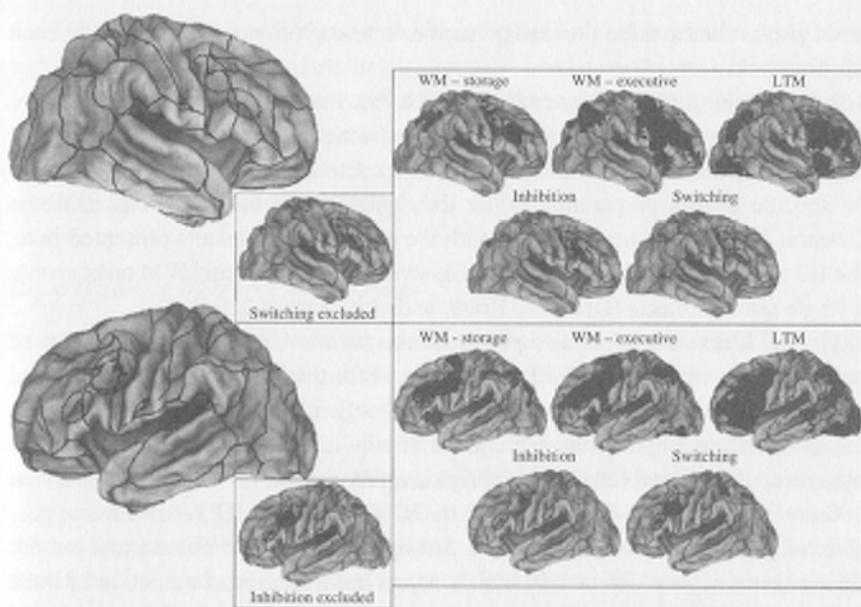
The energization account of DMJ activity, which implies selection and strengthening of behavioral responses and/or their related task sets, may be contrasted with a conflict-monitoring account (Carter, et al. 1998; MacDonald, et al. 2000; Botvinick, Cohen, and Carter 2004), which implies only an indirect link to the control of behavior. Additional evidence for energization, as opposed to conflict monitoring, comes from studies that directly pit manipulations of conflict at the response selection stage against manipulations of conflict at prereponse selection (perceptual and semantic) stages. A growing body of studies has found that the DMJ region responds to increasing demand on response selection but

not to other forms of "conflict" (Milham et al., 2001; Nelson, et al. 2003; Liu, et al. 2006). Other studies have found evidence that the DMJ can be recruited in anticipation of response conflict, before the target stimulus is presented, and that anticipatory activation is correlated with reduced interference (Stern, et al. 2007). As mentioned previously, the DMJ appears to overlap with both the CMAR and the pre-SMA in the monkey, which have strong connections to motor cortex and some direct projections to spinal motor neurons (Dum and Strick 1991), further supporting the argument that the DMJ is involved in higher-order contextual control and initiation of response selection. In addition, some researchers have reported that lesions of dorsal cingulate do not specifically impair performance on "cognitive control" tasks (Fellows and Farah 2005). These diverse types of evidence are difficult to explain with a conflict-monitoring account but are consistent with a behavioral "energization" account. Although the pattern of anatomic projections from DMJ strongly implicates motor control, the anatomic inputs to the DMJ also imply a role for incentive-based or motivationally based action selection. The CMAR receives input from a wide variety of limbic structures, including the rostral temporal cortices, insula, retrosplenial cortex, and OFC (Morecraft and van Hoesen 1998). In humans and animals, the pre-SMA appears to be particularly important for internally generated behaviors (Goldberg 1985; Passingham, Chen, and Thaler, 1989). Like the concept of internally generated actions, the energization concept implies that the activation of task goals or motor plans by DMJ is partly a function of incentive, which is consistent with evidence from primate studies linking the cingulate motor fields to reward-based action selection (Shima and Tanji 1998).

What is appealing about the energization account of the function of the DMJ is that it provides a simple explanation for why this region seems to be activated in nearly any task condition requiring greater cognitive effort. To the extent that a given task of any sort requires incentive-driven energization of response selection, the energization view predicts greater activation of DMJ. The ubiquity of DMJ activation in the cognitive neuroscience literature supports this view. Though positing that the DMJ subserves energization makes precisely the same predictions as a view that says it is simply involved in more effortful tasks, "effort" is not in itself a function and gives no explanation of why a particular brain region should exhibit greater activation in all cases of more effortful cognitive processing. The energization view put forward by Stuss and Alexander (2007), on the other hand, provides a neurophysiologic explanation for why recruitment of a discrete brain region may occur under such a wide array of task demands.

#### *Inferior Frontal Junction*

As shown in Figure 4-4, the only other region activated in all of the cognitive meta-analyses is the left inferior frontal junction (IFJ), so-called because it lies at



**FIGURE 4-4.** Conjunction images of the meta-analytic results for WM storage, WM executive, LTM, inhibition, and task-switching shown on the lateral surface of the brain. Insets show the activated regions in each individual domain. The anterior-most region indicated with a dotted line is the posterior portion of the IFG, and the more posterior and superior region is the IFJ.

the junction of the inferior frontal sulcus and the premotor sulcus, encompassing superior BA 44, posterior BA 46, and mid-lateral BA 6. In our meta-analyses, the right IFJ was active in all of the cognitive domains except task-switching (i.e., Nee, Wager, and Jonides 2007; Wager and Smith, 2003; Wager, unpublished data), whereas the left IFJ was active in each of these domains as well task-switching (Wager, Jonides, and Reading 2004). This region was also found to be active bilaterally across a range of task-switching, set-shifting, and S-R reversal studies, as well as in the left hemisphere in Stroop tasks, in a recent meta-analysis by another group (Derrfuss, Brass, Neumann, and von Cramon 2005). Finally, a recent study comparing different types of attention switching in the same individuals showed event-related activation of IFJ, especially in the left hemisphere, related to shifts both between objects and object attributes, and shifts between both visible stimuli and stimuli held in WM (Wager, Jonides, Smith, and Nichols 2005).

As alluded to at the beginning of this chapter, this region makes up at least a part of the DLPFC region proposed to subserves manipulation of the contents of WM. However, this interpretation cannot account for why this region is activated during response inhibition and task-switching, as well as in WM and LTM tasks that do not require manipulation of the contents of WM. Consequently, the IFJ

must play some broader, domain-general role in cognition that is needed in each of these tasks.

Neuroimaging studies have demonstrated that this region is specifically active during the presentation of a cue that indicated which of two tasks the subject had to perform (Brass and von Cramon 2002), an activation that was later shown to be specific to task preparation rather than encoding of the cue (Brass and von Cramon 2004). In addition, in line with the meta-analytic results presented here, the IFJ was found to be active across task-switching, Stroop, and WM tasks within a single set of subjects (Derrfuss, Brass, and von Cramon 2004).

Human lesion work has also produced results consistent with the findings of neuroimaging studies described above, at least for the left hemisphere. Stuss and Alexander (2007) show that patients with damage in and around this IFJ region exhibit selective impairments in a number of conditions that can be best explained by a difficulty in establishing an appropriate task set: (a) false alarms on the first 100 trials, but not the subsequent 400 trials, of a complex RT task with five possible responses; (b) false alarms in a Stroop-like task; (c) false alarms, but not false negatives, in an RT task in which targets are a specific conjunction of three features; (d) difficulty establishing the correct response set in the Wisconsin Card Sorting Task, as indexed by an error after three consecutive correct responses; (e) false alarms in a word recall task; and (f) false alarms on a no-go task.

Consequently, both functional neuroimaging and human lesion studies have suggested that this region, at least in the left hemisphere, is involved in "task-setting" (Stuss and Alexander 2007) or "updating of task representations" (Derrfuss, et al. 2005). Although the details vary slightly, both of these interpretations propose that this region sets up S-R mappings in other cortical regions that facilitate appropriate responding based on the specific demands of the task (essentially the prefrontal cognitive control function proposed by Miller and Cohen [2001]), a putative function that is consistent with the broad range of cognitive domains that result in activation of this region in our meta-analytic data.

One issue that has not yet been fully resolved is whether this task-setting function is subserved specifically by the left IFJ or if it is subserved by the IFJ bilaterally, although the evidence seems to be in favor of some degree of left lateralization of this function. First, our meta-analytic data for task-switching failed to reveal activation of the right IFJ (Wager, Jonides, and Reading 2004), and although the meta-analysis by Derrfuss, et al. (2005) did reveal activation of right IFJ, the activated region was substantially smaller than that observed in the left hemisphere. Given that task-switching paradigms should be a canonical case of task-setting, inconsistent activation of the right IFJ in task-switching suggests that the right IFJ is less involved in task-setting than is its contralateral homologue. Second, individual functional imaging studies typically find that left IFJ activation is more prominent during task-switching (Sylvester, et al. 2003; Wager, Jonides, and Reading 2005). In addition, whereas the initial report by Brass and

von Cramon (2002) revealed cue-specific activation of both left and right IFJ in a task-switching paradigm, when they isolated the need to switch task set from simple presentation of the cue, only left IFJ activation was apparent (Brass and von Cramon 2004). Finally, and perhaps most tellingly, the behavioral task-setting impairments in lesion patients described by Stuss and Alexander (2007) were selective to lesions in the left hemisphere.

#### *Right Posterior Inferior Frontal Gyrus*

Another prefrontal region that is commonly activated in cognitive tasks is the posterior portion of the inferior frontal gyrus (IFG), specifically the region including mid-posterior BA 46, superior BA 45, and mid-anterior BA 44 in the right hemisphere (see Figure 4-4). This region is active during LTM (Wager, unpublished data), response inhibition (Nee, Wager, and Jonides 2007), and WM storage and executive tasks (Wager and Smith 2003), but unlike the DMJ and IFJ, activation of this region is notably absent during task-switching (Wager, Jonides, and Reading 2004). In perhaps the largest fMRI study of task-switching to date, we scanned 40 individuals chosen from a group of more than 250 to be either high or low in RT switch costs (Wager, Jonides, and Reading 2005), and IFG activity was inconsistent across switch types. Bilateral IFG activation was elicited by switching between objects held in WM, or between visible object attributes, but not when switching between attributes in WM or visible objects. One explanation is that some kinds of switch may have loaded more heavily on selection and/or inhibition among competing representations. In contrast, another study from our laboratory of three different tasks that place high demand on response selection/inhibition all showed right IFG, but not left IFG, activation (Wager, Sylvester et al. 2005).

An emerging consensus in the literature is that right IFG is related to late-stage (i.e., motor) response selection, whereas left IFG is more related to selection among semantic representations or concepts held in WM. Nee, Wager, and Jonides (2007) used a logistic regression strategy to examine the relation between selection demand at different stages of processing (stimulus, response selection, and motor execution) and brain activity in studies of cognitive control and found that stimulus-related selection demand and selection among verbal materials predicted left IFG activity, whereas late-stage demand for selection in response execution predicted right IFG activity. This dissociation is consistent with other recent syntheses that link left IFG with semantic selection (Poldrack, et al. 1999) and right IFG with motor inhibition (Thompson-Schill, et al. 1997; for review, see Aron, Robbins, and Poldrack 2004).

Other neuroimaging studies of response inhibition, particularly those that emphasize demand on inhibition of already-initiated responses, have also consistently demonstrated activation of the right IFG (e.g., Garavan, Ross, and Stein 1999; Rubia, et al. 2003), and response inhibition has been shown to be selectively

impaired by damage to the right IFG in humans (Aron, et al. 2003). With this in mind, a plausible interpretation of activation of this region by LTM and WM storage and executive tasks is that these tasks also require both stimulus and response selection processes for their successful performance.

### Common activations across memory tasks

Here we discuss regions of prefrontal cortex that were active in more than one of the three memory contrasts investigated in our meta-analyses (i.e., WM storage, executive WM tasks, and LTM) but that were not active in either inhibition or task-switching. Thus, regions discussed in this section likely reflect processes specifically related to holding information in mind or otherwise carrying out processing on that information.

Before discussing brain regions active in both WM and LTM tasks, it is important to consider the extent to which LTM and WM reflect truly dissociable memory systems. A nascent view in cognitive neuroscience is that WM actually reflects a reactivation of information stored in LTM (Ranganath and Blumenfeld 2005; Jonides, et al. 2008). Whereas the classic view that WM and LTM are distinct forms of memory is supported by numerous demonstrations of double dissociations in studies of patients with lesions of the medial temporal lobe (exhibiting selective LTM deficits), perisylvian cortex (exhibiting selective WM deficits), and the frontal lobe (exhibiting greater WM deficits), Ranganath and Blumenfeld (2005) have marshaled an impressive array of evidence that poses a serious challenge to the classic view. The LTM tasks used in these studies have typically required encoding of material that is semantically meaningful (e.g., words), whereas WM tasks have often required repeated short-term maintenance of material without semantic meaning (e.g., strings of letters or digits). Ranganath and Blumenfeld summarize a substantial amount of data showing that patients with medial temporal lobe lesions do exhibit severe deficits in WM tasks that use novel materials (e.g., trial-unique stimuli, rather than the same set of letters or numbers repeated a large number of times throughout the task), that patients with perisylvian lesions have deficits in LTM tasks if study items are not semantically meaningful, and that lesions of prefrontal cortex do not produce a specific deficit in either WM or LTM but rather interfere with cognitive control processes typically brought to bear in both types of task.

With these objections in mind, Jonides et al. (2008) review the available data on WM and present a neurobiologically grounded model that essentially proposes that the actual representations of to-be-remembered items occur in posterior cortical regions and are bound together or associated with each other to form a memory trace by the hippocampus, and that prefrontal cortical regions subserve control processes relevant to encoding and retrieval of this information as well as other aspects of task performance (e.g., attention and response selection).

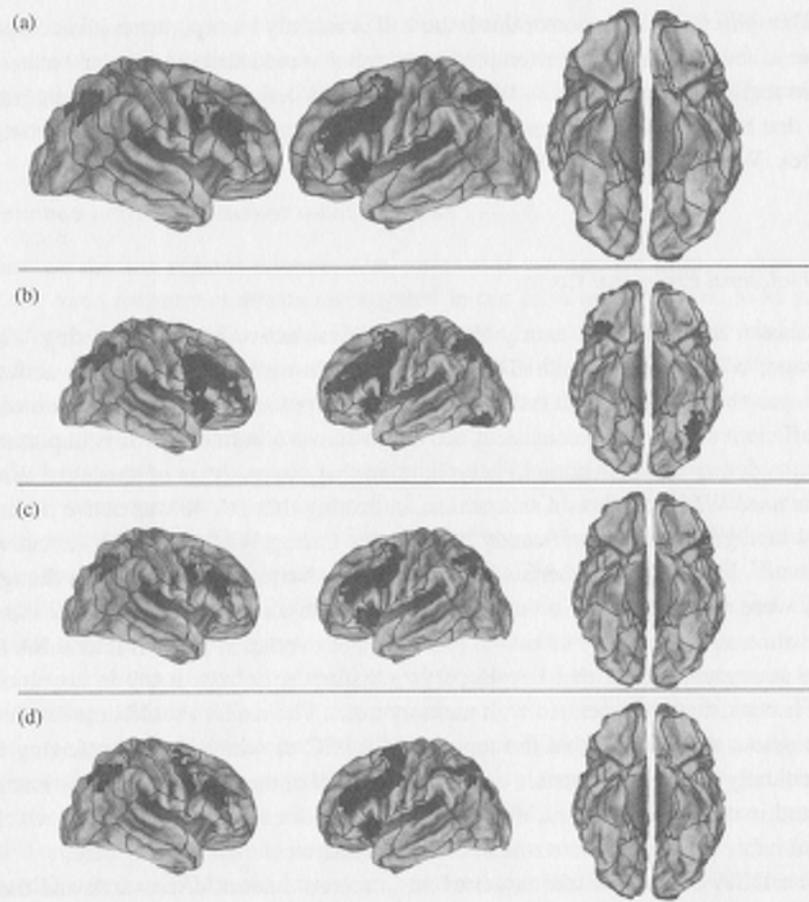
Though a final resolution of this issue will ultimately incorporate evidence from diverse sources, and is not attempted here, we observed striking overlap between brain regions activated in both WM and LTM tasks in our meta-analyses, suggesting that both types of tasks use common brain systems, particularly in the frontal cortex. We discuss these commonalities below.

### *Dorsolateral Prefrontal Cortex*

As shown in Figure 4–5, nearly all of BA 46 was active bilaterally during WM storage, WM executive, and LTM tasks, but as shown in Figure 4–4 this activation was absent during both task-switching and response inhibition (i.e., there was insufficient evidence for consistent activation across laboratories). It is important in considering this activation to keep in mind that our analyses of executive WM tasks used WM storage as a subtraction, indicating that BA 46 was active during WM storage but was significantly more active during WM tasks with executive demands. Furthermore, whereas BA 9 and 46 are frequently discussed as though they were a single region in the literature, our meta-analytic results clearly show activation in the majority of BA 46 that does not overlap at all with lateral BA 9. This strongly suggests that BA 46 plays a distinct role from BA 9 in cognition that is consistently associated with memory tasks. The reader should bear in mind throughout this section that the region of DLPFC to which we are referring is specifically the area activated in common across all of the memory domains investigated in our meta-analyses, namely BA 46, and does not include BA 9, which presumably plays a separate role in cognition that we do not address here.

The DLPFC has been the target of an immense amount of research and theory in the past several decades, a thorough review of which is not possible here. However, a number of authors working in various literatures have now proposed that one of the functions of this region is to activate task-relevant representations in posterior cortex, thus establishing a processing bias toward relevant material (Miller, Erickson, and Desimone 1996; Desimone 1998; Hopfinger, Buonocore, and Mangun 2000; MacDonald, et al. 2000; O'Reilly, et al. 2002; Curtis and D'Esposito 2003; Pasternak and Greenlee 2005; Ranganath and Blumenfeld 2005; Ranganath 2006; Jonides, et al. 2008). In WM rehearsal, BA 46 might serve to repeatedly reactivate or "refresh" posterior representations of to-be-remembered material (Raye, et al. 2002; Johnson, et al. 2005).

By this view, the representation of information in posterior cortices (e.g., semantic information in the temporal lobe, visual information in inferior temporal and/or occipital cortices, spatial information in parietal cortex, and so on) must be periodically refreshed so that it is not lost due to decay or interference. Demonstrations of delay-period activity of cells in primate DLPFC during delayed-match-to-sample are now classics in the field (e.g., Funahashi, Bruce,



**FIGURE 4-5.** Conjunction images of the meta-analytic results for all of the memory domains investigated here, shown on the lateral, medial, and ventral surfaces of the brain. (a) WM storage, WM executive, and LTM. (b) WM executive and LTM. (c) WM storage and LTM. (d) WM storage and WM executive.

and Goldman-Rakic 1989; Fuster 1973), and whereas these findings were initially interpreted as reflecting the actual storage of information in WM in DLPFC (Goldman-Rakic 1987), this interpretation has been challenged by evidence that cells in posterior cortices are also active during the delay in these tasks and that delay-activity is consistently observed in cortical regions that are known to be involved in the perceptual processing of the stimulus features critical for task performance (for review, see Pasternak Greenlee 2005). Thus, in standard (visual) non-match-to-sample tasks, cells in inferior temporal cortex exhibit delay activity, whereas tasks in which the direction of motion of a visual stimulus must be remembered result in delay activity in area MT, somatosensory WM tasks result

in delay-related activation of primary and secondary somatosensory cortex, and similar results have been found for auditory cortex and WM for tones (Pasternak and Greenlee 2005). However, the lateral prefrontal cortex, unlike posterior cortex, seems to be critical for maintaining representations over a delay period when distractors are presented, consistent with a role in refreshing posterior representations and making them robust to interference (Miller, et al. 1996). In another study, reversible deactivation of DLPFC (via cooling) disrupted delay-related activity in inferior temporal cortex during a visual WM task (Fuster, Bauer, and Jervey 1985).

This interpretation of the role of BA 46 is consistent with our meta-analytic data, in that one would expect that a brain region responsible for maintaining representations in posterior cortices would need to be recruited after retrieval of information from LTM (in order to keep the information online to guide accurate responding) as well as during the maintenance of information in simple WM storage tasks. Furthermore, relatively greater activation of this region can be expected in WM tasks with executive demands than in simple storage tasks, insofar as tasks that demand manipulation of information in WM presumably require the temporary maintenance of additional intermediate states in the transformation process (e.g., given the demand to alphabetize a set of four letters stored in WM, a series of intermediate states would need to be represented given that the subject is, presumably, unable to alphabetize the entire set simultaneously). In essence, then, manipulation of information in WM inherently creates interference and thus requires DLPFC. In this regard, it is worth noting that patients with lesions in this area have been shown to be particularly susceptible to distraction when performing WM tasks (Chao and Knight 1998).

Manipulation of information in WM requires additional scheduling and operating processes as well, which may require more anterior portions of DLPFC (e.g., BA 9 and 10), which we discuss later. Because simple "refresh" operations (Raye, et al. 2002; Johnson, et al. 2005) and simple selective attention tasks (Hopfinger, Buonocore, and Mangun 2000; Weissman, Warner, and Woldorff 2004) are sufficient to elicit BA 46 activation, we associate the region with elemental top-down biasing operations rather than with more complex processes.

If top-down biasing recruits BA 46, one can ask why it is not more reliably activated in task-switching and inhibition studies. Though both types of tasks require top-down biasing for successful performance, the control conditions in these tasks (e.g., nonswitch trials in mixed switch/nonswitch task blocks) are likely to recruit BA 46 as well. Thus, the top-down biasing view would not predict differential activation of this region in experimental and control conditions in many switching and interference-resolution studies.

In addition, it is worth noting that the Nee, Wager, and Jonides (2007) meta-analysis reported here also examined activated regions in several inhibition tasks separately (whereas we report only on those regions significantly activated across

all the task types) and found activation of BA 46 in go/no-go and Stroop tasks. Based on an individual study (de Zubicaray, et al. 2000) that demonstrated longer RT and fewer errors, along with greater DLPFC activation, as the proportion of no-go trials in the task increased, Nee, Wager, and Jonides interpreted their DLPFC activation in go/no-go tasks as reflecting the deployment of greater control during a "response selection" phase prior to initiating a response. This interpretation is in line with the view of the role of DLPFC taken here, in that during the performance of a go/no-go task with a high proportion of no-go trials, an efficient strategy may be to devote extra processing resources to the stimuli themselves, which may require additional strengthening of representations of the stimuli in posterior cortices via top-down biasing by the DLPFC. Likewise, activation of the DLPFC by Stroop tasks is to be expected because the ability to respond correctly on incongruent trials specifically requires enhancing relevant representations and/or inhibiting irrelevant ones.

Finally, it is interesting to note that the putative roles of DLPFC and the IFJ as presented in this chapter have an intuitively appealing relationship to each other given their anatomic proximity; namely, that DLPFC maintains task-relevant representations in posterior cortices (whether these representations were retrieved from LTM or have been actively maintained since the stimulus presentation), whereas the immediately posterior IFJ sets up S-R mappings, or a "task-set," in order to produce the correct behavioral responses to stimuli. This raises the (admittedly speculative) possibility that stimulus information being maintained via top-down control from the DLPFC is passed from the DLPFC to the IFJ, which then influences the development of motor plans in the supplementary motor area (SMA) that lie immediately posterior to the IFJ. This foreshadows a view of prefrontal cortex function that posits an anterior-to-posterior gradient of hierarchical information processing that will be taken up in greater detail in the final section of this chapter.

#### *Left Anterior and Middle IFG*

Figure 4-5c also reveals activation of the left anterior and middle IFG, BAs 47 and 45 respectively, in LTM and WM storage tasks. Functional neuroimaging studies have demonstrated greater activation of this region of the left IFG under conditions that require greater controlled retrieval from episodic memory (Wheeler and Buckner 2003), greater selection demands on information retrieved from semantic memory (as discussed earlier in the section "Right Posterior Inferior Frontal Gyrus"; Thompson-Schill, et al. 1997), and the resolution of proactive interference in WM (Badre and Wagner, 2005; Jonides and Nee, 2006).

Recent evidence suggests that BA 47 and 45 make distinct contributions to the cognitive control of memory that are consistent with our meta-analyses as well as with the individual studies mentioned above (Badre and Wagner 2007). Whereas

our meta-analytic data do not dissociate activation in these regions, Badre and Wagner argue that anterior IFG is involved in controlled retrieval of information from memory while mid-IFG is involved in postretrieval selection; that is, the selection of task-relevant features of a retrieved memory (assuming that not all of the information brought to mind during a recall attempt will be task-relevant), a view that we alluded to when discussing the role of right IFG in response inhibition. Critically, this same postretrieval selection mechanism is presumed to resolve proactive interference in WM tasks, and indeed activation of this region is correlated with behavioral measures of proactive inhibition (Badre and Wagner 2005). Thus, when a negative probe that was part of the target set on a preceding trial is presented (i.e., a probe in a WM task to which the correct answer on the current trial would be "no," but to which the correct answer on the preceding trial would have been "yes"), episodic information relevant to the preceding trial is automatically retrieved, and the participant must select between multiple active representations (of the current and preceding trial) in order to respond appropriately.

#### *Anterior Lateral Prefrontal Cortex*

As shown in Figure 4-5b, portions of BA 10, or anterior lateral prefrontal cortex (ALPFC), were active during both LTM and WM executive tasks. Although activation of this region was relatively limited in extent and largely lateralized to the right hemisphere, it is important to keep in mind that the sinus cavities generate susceptibility artifacts in the fMRI signal in frontopolar and orbitofrontal regions, leading to signal distortion and dropout in many studies (Wager, et al. 2007).

A number of theories regarding ALPFC function have been proposed that vary in their details, but all have in common the notion that ALPFC operates at the top of a processing hierarchy in cognition such that it performs operations on, or selects between, task representations in more posterior regions of the lateral prefrontal cortex, such as the DLPFC (Koechlin, et al. 1999; Christoff and Gabrieli 2000; Braver and Bongiolatti 2002; Koechlin, Ody, and Kouneiher 2003; Christoff and Keramian 2007). Thus, activation of ALPFC is generally found during the performance of tasks that require subjects to generate subgoals (Koechlin, et al. 1999; Braver and Bongiolatti 2002) or to perform cognitive operations on internally generated information (Christoff and Gabrieli 2000; Christoff and Keramian 2007), or in other words when processing needs to be carried out on the results of prior processing on task-relevant stimuli.

Such a high-level goal selection or subgoal system might play a role in optimizing performance in many tasks, which is a potential cause of ambiguity in mapping brain activity patterns to specific task types. For example, we have found task-switching-related activation of ALPFC, particularly when switching among multiattribute objects stored in WM (Wager, Jonides, et al. 2005). In addition, we have found that activity in right BA 10 is correlated with successful preparation

for upcoming conflict in a Stroop-like task (Stern, et al. 2007). In the switching case, subgoals might be involved in simultaneously coordinating rehearsal of objects in WM and shifting tags for behavioral relevance from one object to another. In the conflict case, BA 10 might have been recruited by participants who engaged in voluntary strategies to select one stimulus dimension before it appeared.

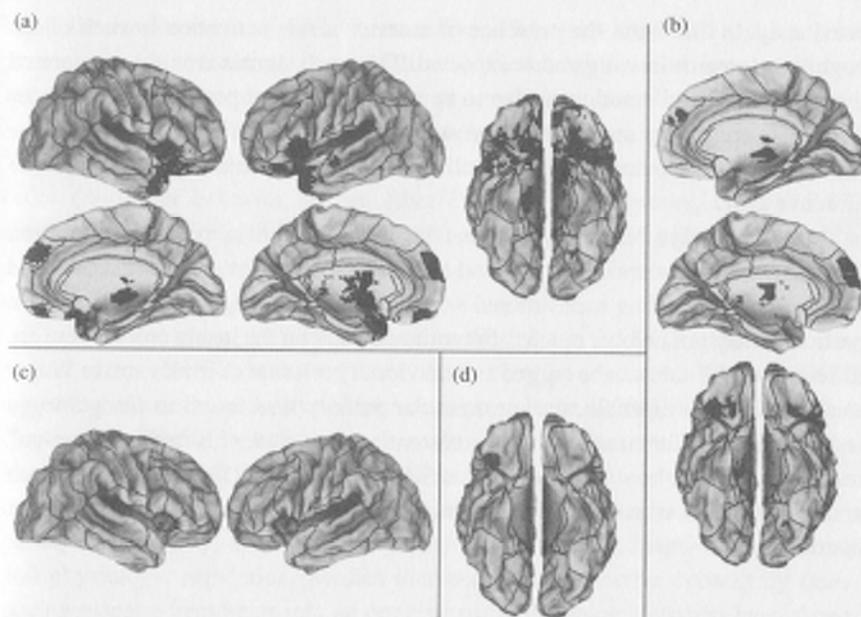
In this view, activation of this region by executive WM is expected, in that these tasks all require processing to be carried out on internal representations of stimuli maintained in WM. Activation of this region in LTM, however, is somewhat less clear-cut. Nonetheless, an explanation of why this region is active in LTM tasks emerges from an early meta-analytic review showing that activation of this region is nearly ubiquitous in recall tasks but frequently absent in recognition tasks (Christoff and Gabrieli 2000). Thus, recognition does not recruit ALPFC because the participant need only evaluate the familiarity of a presented stimulus, whereas during recall tasks the subject must engage in controlled retrieval (presumably subserved by the left frontal operculum, as discussed earlier) and then evaluate whether the retrieved information is in fact task-relevant (i.e., that it was actually learned in the context of the experiment), and this latter process results in activation of ALPFC.

### Common activations between emotion and cognitive domains

#### *Anterior Insula*

As can be seen in Figure 4–6, a portion of the dorsal anterior insula and underlying frontal operculum was activated in most of the cognitive tasks for which we have meta-analytic data. A complication is that activations in many cognitive studies that report activity in IFG appear to be localized at least partially in the operculum and insula, which are very nearby lateral IFG in three-dimensional anatomic space. It is only by comparing activation coordinates across many studies that the consensus across them becomes appreciable. This consensus is that the centroids of activity across many studies lie in the bilateral folds between the frontal operculum and dorsal anterior insula, and these foci may be separable from those on the lateral surface of the IFG. Individual studies in our laboratory have borne out this conclusion as well: the three response-inhibition tasks studied in Wager et al. (2005) activated various parts of insula and IFG, but the superior insular/opercular junction was the area consistently activated across all three tasks. In addition, activity in this area was consistently correlated with higher behavioral interference costs. Nonetheless, it is possible that some of the IFG-related findings discussed above apply to the insula and/or operculum.

Despite being frequently observed in studies of cognition, activation of the anterior insula has received relatively little attention in the cognitive



**FIGURE 4–6.** (a) Regions active in the meta-analysis of experienced emotion. (b) Regions activated during experienced emotion and LTM. (c) Regions active during experienced emotion, LTM, executive WM, and task-switching. The region indicated with a dotted line is the dorsal anterior insula. (d) Orbitofrontal cortex activation observed during experienced emotion, LTM, and executive WM.

literature—perhaps for the reasons mentioned above. Whereas activation of this region is commonly observed in studies of emotion, its role in cognition is not well understood. In our meta-analytic data, however, a common region of the anterior insula is activated during experienced emotion, LTM, task-switching, and WM storage and manipulation (in the left hemisphere, and bilaterally if WM storage is excluded).

One view of anterior insula function that is consistent with the activations observed here is that it serves as an interface between valuations of reward carried out by the OFC (see later) and cognitive control processes carried out by the lateral prefrontal cortex (Wager and Barrett 2004). That is, during the performance of a difficult task, the anterior insula may generate signals that either the wrong task is being performed or that the task is being performed in a suboptimal manner. Thus, in this view the anterior insula “informs” lateral prefrontal regions about which stimuli in the environment should be sought out or avoided based on their motivational salience, as determined by OFC, so that these lateral prefrontal regions can maximize reward by appropriately directing cognition via their roles in task-setting, response selection, and related processes, as discussed

previously. In this light, the presence of anterior insula activation in each of the cognitive domains investigated is expected. That such signals would be generated during experienced emotion is also to be expected, in that presumably the experience of a relatively strong affective state would lead to a biasing of cognitive processing toward or away from stimuli or internal representations relevant to the affective state.

Our meta-analytic data suggest that insula activation in response-inhibition tasks appears to be less consistent and right lateralized. If the insula does indeed play a role in signaling motivational salience, then late-stage inhibition tasks in particular may not involve much differential demand on the insula unless there are different stimuli that can be tagged as behaviorally relevant or irrelevant. In Wager et al. (2005), for example, the most insular activity was found in the go/no-go task, in which different stimuli are consistently associated with "go" and "no-go" responses, and the least was found in an S-R compatibility (Simon) task in which a single stimulus is associated with more or less conflict depending on the task instructions.

#### *Orbitofrontal Cortex*

Another region commonly activated during the experience of emotion and the performance of some cognitive tasks, in this case executive WM tasks and LTM, is the OFC. A number of authors (e.g., Bechara, Damasio, and Damasio 2000; Barrett, et al. 2007; Coricelli, Dolan, and Sirigu 2007) have suggested that the OFC acts to integrate sensory information and assign value to stimuli in the environment, which then guides decision making. Many studies from the animal and human literature support this broad view. For example, in monkeys damage to the OFC or its connections with the amygdala disrupts updating of the value of reinforcers, causing the animals to continue to overeat liked foods long after intact animals are satiated (Baxter, et al. 2000). The lesions that produce these effects do not disrupt appetitive behavior and satiety generally. Likewise, humans and animals alike show deficits in adjusting behavioral responses after stimulus-reward contingencies change (Wallis, et al. 2001; Fellows and Farah 2003, 2005).

Some of the original descriptions of the effects of PFC damage appealed to accounts of stimulus-driven behaviors. Studies of "utilization behavior" (L'Hermitte, Pillon, and Serdaru 1986) characterized patients as unable to use high-level-context information to avoid making socially inappropriate responses. Other research focused on the inability to flexibly switch strategies after the "correct" stimulus dimension changes in the Wisconsin Card Sorting and related tasks (Milner 1963). It may be that both of these effects, and similar ones on other tasks, are related to OFC damage. OFC and ventromedial prefrontal cortex (VMPFC) damage are apparent in the brains of L'Hermitte patients, for example. In this

light, the involvement of OFC in executive WM tasks and LTM tasks can be seen as one of evaluating the motivational relevance of stimuli presented during the task in order to direct cognitive processing by lateral prefrontal regions via the anterior insula and dorsal cingulate cortices. By this account, OFC and VMPFC are involved in using layers of context information to establish higher-order control of behavior, as are other PFC regions; however, OFC/VMPFC are concerned specifically with elements of internal reward value (value to the self) and social context, both of which might be termed internal or motivational context.

This account fits in with other literature that places the OFC and medial prefrontal cortex (MPFC) at the top level of a system for context-based control over adaptive behavioral and physiologic responses. Price (2005), for example, has characterized these regions as "systems for survival" and noted their extensive interconnections with limbic regions and related brain-stem centers. These centers include the insula, amygdala, nucleus accumbens, hypothalamus, and brain-stem periaqueductal gray, and collectively they are critical for adaptive motivational and physiologic regulation. Studies that manipulate affective context by introducing placebo treatments into an ongoing pathophysiologic process have shown that MPFC and OFC are the regions most consistently responsive to placebo (Mayberg, et al. 2002; Petrovic and Ingvar 2002; Lieberman, et al. 2004; Wager, et al. 2004; Petrovic, et al. 2005; Zubieta, et al. 2005; Kong, et al. 2006; Price, et al. 2007; Wager, Scott, and Zubieta 2007). These regions are also critical for other kinds of affective appraisals, including voluntary emotion regulation (Beauregard, Levesque, and Bourgouin 2001; Ochsner, et al. 2002, 2004; Goldin, et al. 2008; Kim and Hamann 2007), reward and punishment prediction and prediction errors (Hornak, et al. 2003; Knutson and Cooper 2005; Tobler, et al. 2006; Jensen, et al. 2007), and valenced emotional responses across a range of stimuli and specific emotion types (Devinsky, Morrell, and Vogt 1995; Baxter, et al. 2000; Hornak, et al. 2003; Wager, et al. 2003; Price 2005; Wager, et al. 2008). They are also altered in structure and/or function in a range of affective disorders, including PTSD (Shin, Rauch, and Pitman 2006; Etkin and Wager 2007) and depression (Drevets 2000; Johansen-Berg, et al. 2007).

Comparing the cognitive meta-analyses discussed above with meta-analyses of emotion (Kober, et al. 2008; Wager, et al. 2003, 2008) can provide insight into which brain regions respond specifically when task demands are relevant to one's internal social and motivational context. As Table 4-1 shows, the OFC and MPFC are activated most consistently by emotion-related tasks, though there is overlap with the most complex and strategy-driven among the cognitive tasks we discuss—LTM and executive WM in particular. This may be either because WM and LTM tasks place greater demand on optimizing motivational settings and performance monitoring or because they require more high-level, task goal-related selection processes.

### Dorsomedial Prefrontal Cortex

Notably, experienced emotion and LTM both activate the medial portion of BA 9—the dorsal-most portion of dorsomedial PFC, above the cingulate sulcus and anterior to the typical “cognitive control” DMJ area discussed previously (see Figure 4–6b). Our recent meta-analysis (Kober, et al. 2008) suggests this area is particularly important for the generation and regulation of affective responses, as it was the only cortical area coactivated with both the midbrain periaqueductal gray, a key center for regulating physiologic homeostasis and adaptive emotional reactions, and the hypothalamus, a key area for regulating endocrine and physiologic “stress” responses in the body. This region of the brain has been observed to be active during the active regulation of emotional experience (Ochsner, et al. 2004) and in a number of tasks that involve appraisals of another person’s state of mind (e.g., McCabe, et al. 2001; Rilling, et al. 2004), suggesting that it plays a unique role in the interface between social and situational context and motivated behavior in humans.

### Putting it together: A modular processing hierarchy in prefrontal cortex

The evidence reviewed here suggests that distinct regions of prefrontal cortex subserve discrete functions in cognition that operate together in a modular manner to allow for the successful performance of a range of cognitive tasks. Admittedly, the evidence presented in this chapter is by no means comprehensive, and the putative functions assigned to the various regions of cortex discussed here are speculative to various degrees. However, the overall picture of prefrontal cortex function presented here leads to a conceptualization of a cognitive processing hierarchy that proceeds along an anterior-to-posterior gradient, from (a) representations of stimulus value in the OFC and rostral MPFC, to (b) processing of internal goal and task-hierarchy representations in the ALPFC, (c) top-down biasing of stimulus representation in posterior cortices by DLPFC, (d) representation and updating of specific S-R mapping rules in IFJ and lateral premotor cortex, (e) the motivated planning of overt motor behavior in pre-SMA and cingulate motor areas, and (f) the actual production of behavior in primary motor cortex. This notion of hierarchy is present in related forms in several current models of prefrontal function (e.g., Koechlin, Ody, and Kouneiher 2003; Christoff and Keramatian 2007).

Of course, any kind of processing hierarchy in prefrontal cortex does not proceed in a truly linear fashion. One way to conceptualize cognitive control in the prefrontal cortex is as proceeding from the result of evaluations about the value of various stimuli or internal representations carried out in OFC. These valuations are then passed through the dorsal anterior insula to lateral prefrontal cortex, wherein DLPFC selects representations in posterior cortical regions that are task

relevant and enhances their representation and/or inhibits the representation of task-irrelevant representations. When information needs to be retrieved from LTM, the anterior portion of VLPFC is capable of initiating a controlled retrieval process, and if there are multiple competing active representations, mid-VLPFC is recruited to select between them. The IFJ sets up S-R contingencies based on the current context and directs the development of motor plans in supplementary motor cortex based on these contingencies. If additional processing on activated representations is required, for example the solution of intermediate processing stages or the completion of internally generated subgoals, this is carried out by the ALPFC. Finally, if an incorrect response is generated and detected prior to its execution, the right IFG is brought online to inhibit the actual production of the response, and persistent energization of the entire system is maintained by the DMJ.

Although the putative functions of various regions of prefrontal cortex and their arrangement in a processing hierarchy as outlined above have not been firmly established, one can see that considerable progress in theorizing about the function of human prefrontal cortex has been made since Luria’s time. Luria was able to confidently state that patients with lesions to lateral prefrontal cortex suffer from a “. . . disturbance of selective logical operations” (Luria 1966, p. 287), and we are now able to speculate with considerable specificity about what those operations are and where they are situated in the brain. As with the example of respiration given at the outset of this chapter, the prefrontal cortex is clearly “a complex functional system, effected by a differential dynamic arrangement of nerve cells belonging to different levels of the nervous system,” but it is increasingly clear that, much more than being a single functional system, the prefrontal cortex actually subserves a wide array of “atomic” processes that can be flexibly brought to bear depending on the demands of the current situation in order to give rise to an enormous range of human cognitive and affective processes.

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